Gardasil
Post-Approval Adverse Event Review

Pediatric Advisory Committee Meeting
December 7, 2010

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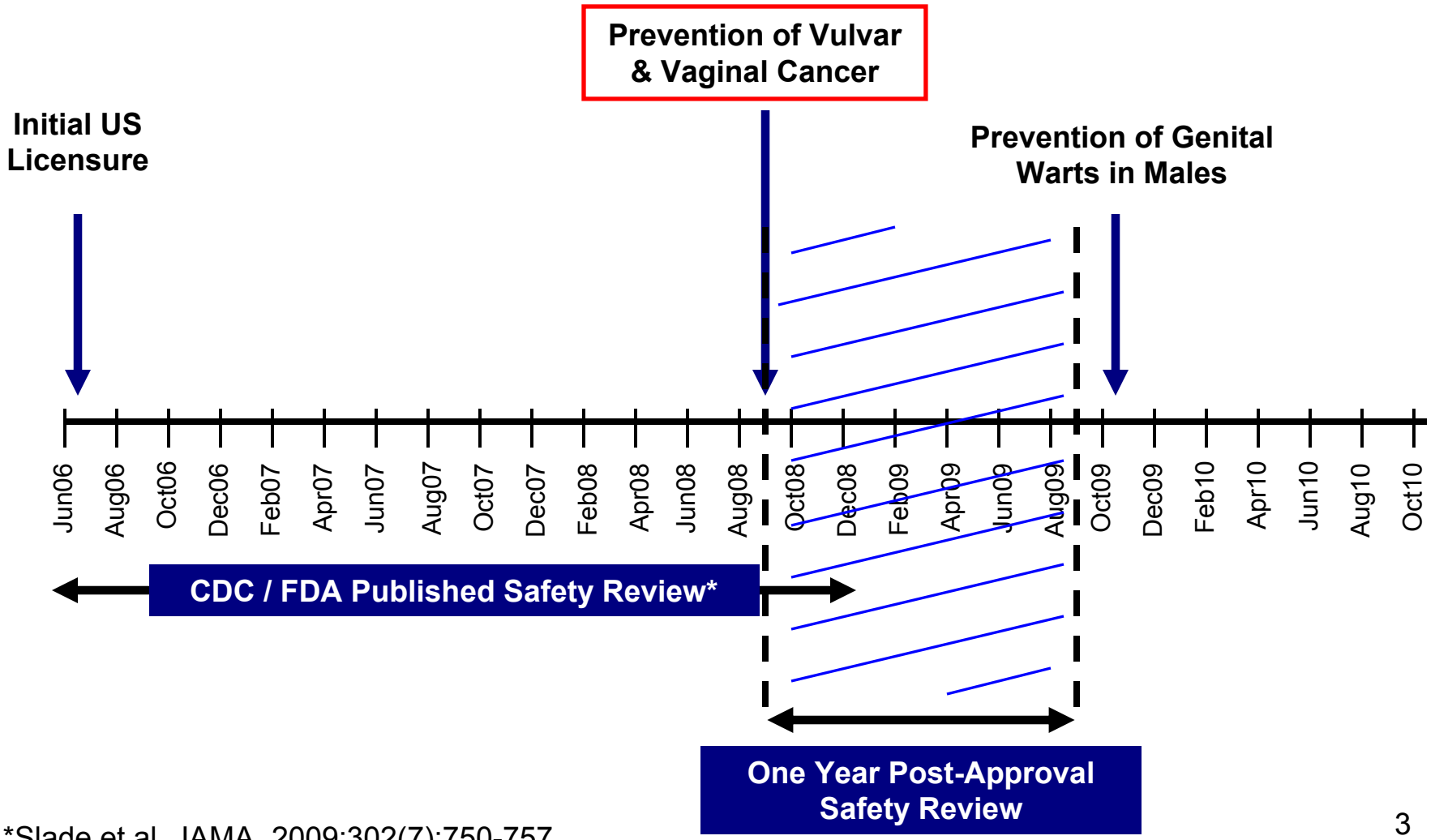
Background

Product	Gardasil, Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant
Formulation	0.5mL suspension for intramuscular injection in a 3-dose series: 0, 2 and 6 months
Manufacturer	Merck & Co.
Current indication and use	1. Females aged 9–26 years: cervical, vulvar and vaginal cancers and related precancerous lesions 2. Females and males aged 9–26 years: genital warts
US Licensure	8June2006
Trigger for PAC Review	12Sept2008

Timeline

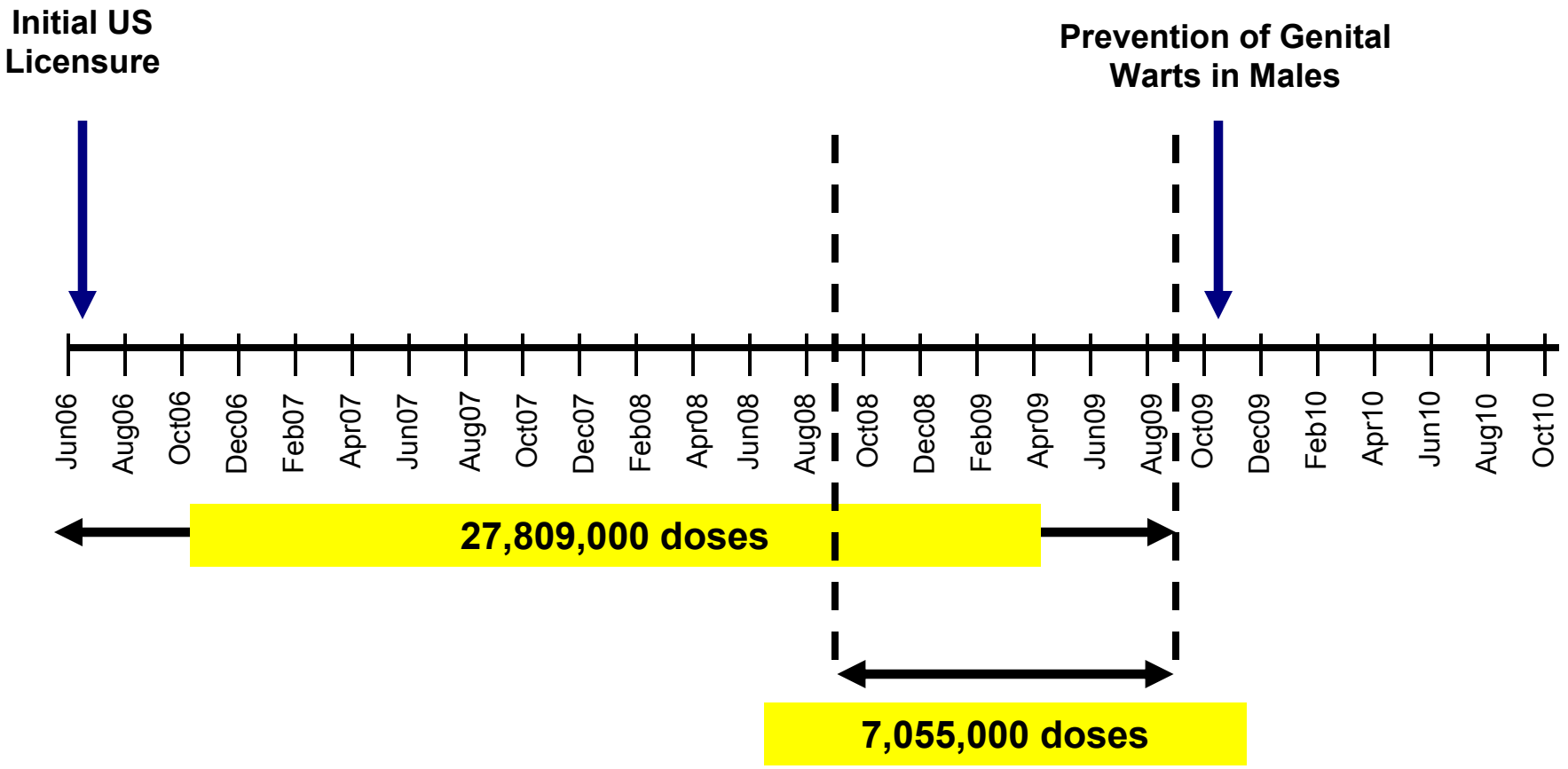
June 2006 – Present



*Slade et al. JAMA. 2009;302(7):750-757

Gardasil Dose Distribution

~75% doses administered in children 9–18 years



Objectives of Safety Review

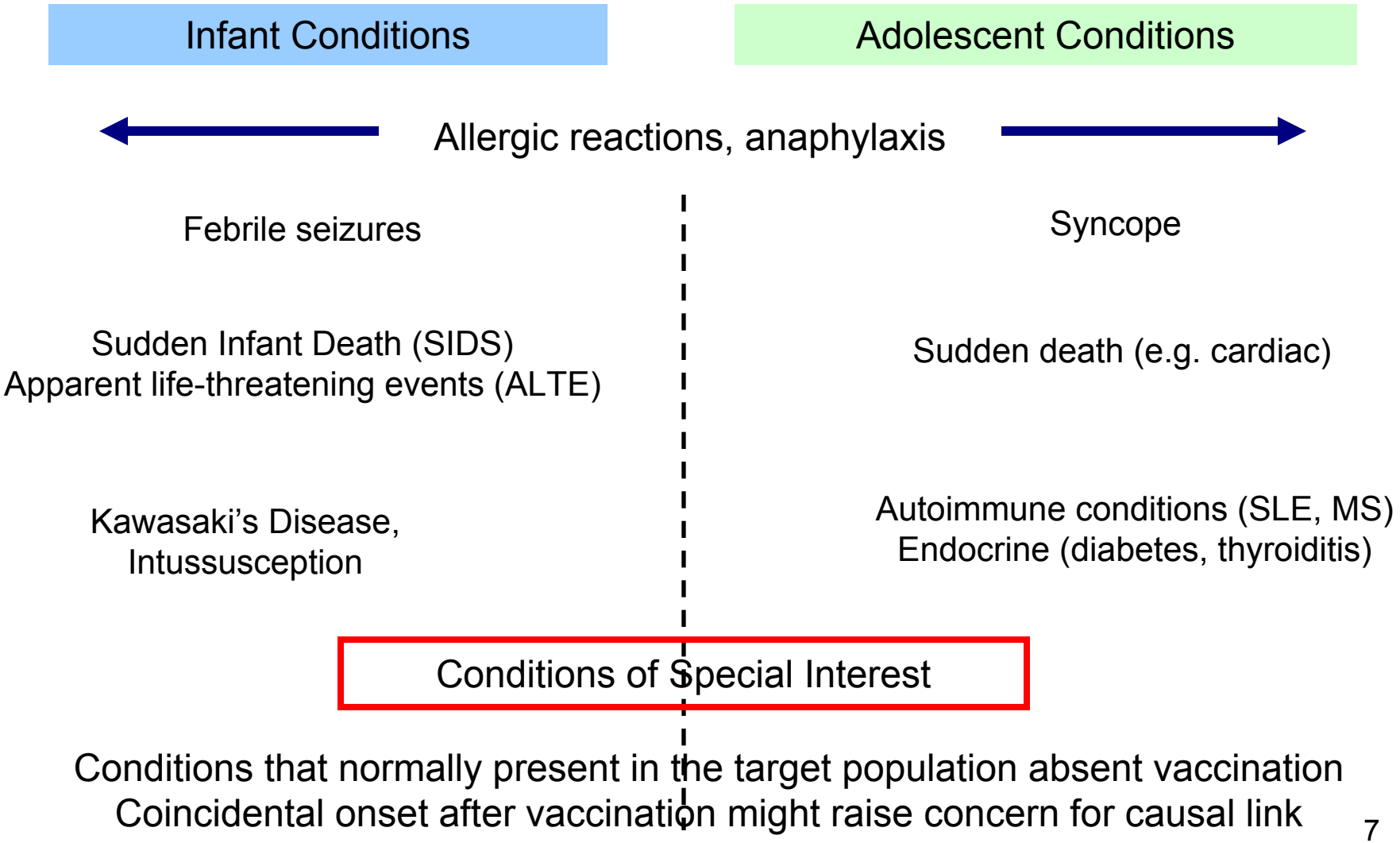
I. Background safety information for Gardasil
- Context for safety surveillance
- CDC / FDA published safety review
- Key findings from observational studies prior to 12Sept2008
- Changes to prescribing information (PI) through 12Sept2008

II. One-year safety review following approval of the new indication
- Summarize VAERS surveillance data among US children aged 0–16 years vaccinated between 12Sept2008–12Sept2009
- Review changes to PI during this time period
- Describe planned and ongoing postmarketing studies

New Context for Vaccine Safety Surveillance

- Introduction of large-scale US adolescent immunization program
  - Between May 2005 and June 2006, 3 new vaccines for adolescents
  - Menactra, Boostrix/Adacel (2005); Gardasil (2006)
  - Creation of 11–12 year-old routine vaccination platform
- New safety surveillance challenges
  - New background of adolescent diseases
  - Limited knowledge of baseline incidence
  - New concomitant medications (contraceptives), disease modifiers (smoking)
- Unique issues
  - HPV sexually transmitted; Gardasil had female-only indication (initially)
  - Existing and successful cervical cancer prevention program
  - Difficult messaging
    - Prophylactic / not therapeutic
    - Efficacy against subset of oncogenic HPV types
    - Lag between infection and cancer onset
  - Rapid inclusion into school-entry mandates
- Stimulated reporting for Gardasil

New Context for Vaccine Safety Surveillance



CDC / FDA Published Safety Summary*

- Postlicensure safety review of first 2.5 years (~23 million doses distributed)
- 12,424 total reports, 94% non-serious
  - Most frequent: syncope, dizziness, nausea, headache, injection site reactions
  - Safety profile described in VAERS consistent with prelicensure data
- 1,896 syncope reports
  - 90% same day of vaccination, over 50% ≤15 minutes of vaccination
  - 15% (293) resulted in falls
  - 11% (200) falls with head injury (45 lacerations, 18 dental injuries, 17 contusions, 9 fractures, 9 concussions, 5 intracranial hemorrhages)
- 47 venous thromboembolism (VTE) reports
  - 66% (31) had sufficient information for review, 32% (15) had no identifiable patient
  - Median age 20 years (range 15–39 years) and median onset interval 23 days (range 0–306 days)
  - 97% (30) occurred after Gardasil alone
  - 90% (28) had ≥1 known risk factor for VTE
    - 20 taking contraception, 10 coagulation disorder, 7 immobility, 2 smokers, 2 pregnant, 1 hyperviscosity syndrome

*Slade et al. JAMA. 2009;302(7):750-757

CDC / FDA Published Safety Summary*

- 32 reports of death
  - 63% (20) had sufficient information for review; 12 with no identifiable patient
  - 70% (14) received Gardasil alone; 9 after dose-1; 5 after dose-2; 6 after dose-3
  - Median age 17 years (range 12–26 years), no clustering by age
  - Median symptom onset interval 14.5 days, (range 2–288 days)
  - Median interval from vaccination to death 14.5 days, (range 2–405 days)
- 19% (6) reports among children ≤ 16 years

Age	Days from Vaccination to Death	Autopsy	Cause of Death
12	63	Not reported	Cardiac arrhythmia secondary to long QT syndrome
14	73	Not reported	Influenza B viral sepsis
15	2	Yes	Cardiomyopathy, arrhythmia
15	45	Yes	Seizure disorder
16	3	Yes	Cardiac arrhythmia
16	15	Yes	Diabetic ketoacidosis and pulmonary embolism

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Vaccine Safety Datalink (VSD)

- Largest active surveillance study for Gardasil
- Used rapid cycle analyses for signal detection for 9 outcomes
  - Aug 2006–Oct 2009
  - 600,558 doses in females aged 9–26 years
  - 416,942 in girls aged 9–17 years
- No safety signals for Guillain-Barre syndrome (GBS), stroke, appendicitis, seizure, syncope, allergic reactions, pancreatitis, anaphylaxis
- Non-significant increased RR 1.98 VTE among girls aged 9–17 years
  - 13 cases electronically identified; 9 chart-confirmed
  - 8 of 9 cases had ≥1 known risk factors (smoking, contraceptive use, obesity, prolonged immobilization, coagulation disorder)
  - Cluster of 4 cases identified on days 2–3 post-vaccination ($P = 0.03$)
  - Self-controlled case series is planned

Postmarketing Study of Gardasil in Females

- Regulatory commitment by Merck agreed upon at licensure

- Kaiser Permanente (KP) California, Aug 2006–Mar 2008
  - Total of 346,972 Gardasil doses evaluated
  - 44,001 female 3-dose recipients aged 9–26 years
  - 189,629 females who received ≥1 dose, (51% aged 9 – 15 years)
  - Some doses administered in Northern California KP overlap with VSD

- Designed as a preliminary tool for detecting potential safety signals
  - No formal hypotheses were tested
  - Active surveillance using ICD-9 codes to identify potential cases, followed by chart review to verify exposures and outcomes
  - For prevalent outcomes, a manageable random sample selected for case review
  - Comparison groups differed by study component

Postmarketing Study of Gardasil in Females

Component	Endpoints	Comparison Group
General Safety	Hospitalizations and ER visits (0, 1–14 and 1–60 days) after each vaccination	180-day post-vaccination self-comparison period
Pregnancy Exposure	Congenital anomalies	Published background rates
Autoimmune conditions	16 prespecified conditions* ≤6 months after each vaccination	Comparison to incidence rates in an unvaccinated group

* Immune thrombocytopenic purpura, autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, diabetes mellitus, Hashimoto's and Graves' disease, multiple sclerosis, acute disseminated encephalomyelitis, other CNS demyelinating conditions, vaccine-associated demyelination, Guillain-Barre syndrome, neuromyelitis optica, optic neuritis, and uveitis.

Postmarketing Study of Gardasil in Females

Component	Major Findings
General Safety	• Elevated risk for syncope on Day 0 and possibly cellulitis on Day 1–14 – 6.6 cases syncope per 100,000 doses – 13.5 cases cellulitis per 100,000 doses • No elevated risk detected for VTE or GBS • No unusual patterns were detected among 14 deaths*
Pregnancy Exposure	• 3.6% (24/665) rate of confirmed congenital anomalies among Gardasil-exposed pregnancies (background rate of ~3.0%). • No elevated risk detected. No apparent pattern among anomalies.
Autoimmune conditions	• 11 out of 16 prespecified outcomes had new-onset cases for evaluation† • No elevated risks were detected

* Burkitt's lymphoma (1); cardiorespiratory arrest secondary to congenital heart disease (3); drug overdose (1); motor vehicle crash (2); respiratory arrest (1); suicide (4); systemic lupus erythematosus (1); and pneumonia (1)

† No incident cases of GBS, autoimmune hemolytic anemia, demyelination and neuromyelitis optica

Cumulative Changes to PI

June2006 – Sept2008

Section	Specific Change to Prescribing Information
Adverse Reactions	Added nausea, dizziness to "Vaccine-related Injection-site and Systemic Adverse Experiences" table
Postmarketing Experience	• **Blood and lymphatic system**: Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy. • **Respiratory, thoracic and mediastinal**: Pulmonary embolus. • **Gastrointestinal**: Nausea, pancreatitis, vomiting. • **General disorders and administration site conditions**: Asthenia, chills, death, fatigue, malaise. • **Immune system**: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria. • **Musculoskeletal and connective tissue**: Arthralgia, myalgia. • **Nervous system**: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope sometimes resulting in falling with injury, transverse myelitis. • **Vascular**: Deep venous thrombosis.

Changes to PI made primarily in response to VAERS data

Syncope Description in Gardasil PI

"Syncope (fainting) may follow any vaccination, especially in adolescents and young adults and it has occurred after vaccination with GARDASIL, so vaccinees should be observed for approximately 15 minutes after administration of GARDASIL."

"Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. **Syncope, sometimes associated with falling**, has occurred after vaccination with GARDASIL. Therefore, vaccinees should be observed for approximately 15 minutes after administration of GARDASIL."

"Syncope has been reported following vaccination with GARDASIL and **may result in falling with injury**; observation for 15 minutes after administration is recommended."

Bold-faced type added for presentation clarity only

Contraindications and Pregnancy Sections
(Unchanged from Original PI)

- Contraindications
  - "Hypersensitivity, including severe allergic reactions to yeast."
- Pregnancy
  - "Gardasil is not recommended for use in pregnant women."
  - Category B: "Reproduction studies have been performed in female rats at doses equivalent to the recommended human dose and have revealed no evidence of impaired female fertility or harm to the fetus due to Gardasil. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, Gardasil should be used during pregnancy only if clearly needed."
  - "Physicians are encouraged to register pregnant women exposed to Gardasil by calling 1-800-986-8999 so that Merck can monitor maternal and fetal outcomes."

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Signal Detection Methods in VAERS

- Manually review all serious reports daily
  - Identify serious and unexpected adverse experiences
  - Create case series and analyze for unusual patterns or trends
  - Generate periodic adverse reports (monthly, quarterly, semi-annual)
  - Continuously monitor conditions of special interest
- Apply statistical methods
  - Calculate reporting rates based upon doses distributed
  - Analyze for disproportional reporting, comparing observed to expected rates of reporting
- Survey and review all published case reports and safety studies
- Correlate findings with manufacturer safety data
- Collaborate with CDC on case review and public messaging

Gardasil Reports in VAERS
12Sept2008 – 12Sept2009

	Serious*		Deaths		Non-Serious		TOTAL	
	US	Total	US	Total	US	Total	US	Total
All Ages	317	942	4	14	1,802	2,046	2,119	2,988
0 – 16 Years	151	489	2	8	1,015	1,085	1,166	1,574

* Serious events include death, life-threatening experiences, inpatient hospitalization or prolongation of hospitalization, or persistent disability.

VAERS Reports of Death

12Sept2008–12Sept2009, Children 0–16 Years

Cause of Death	Concomitant Vaccinations	Notes
Non-injection site necrotizing fasciitis with septic shock	Vaqta, Menactra, Boostrix	11 year old girl with fever 103°F, difficulty walking and hip pain 1 day after vaccination (deltoid) and died 4 days later. Blood culture grew streptococcus pyogenes. Autopsy diagnosis left lower extremity necrotizing fasciitis.
Sudden unexpected death in epilepsy	Flumist	13 year old girl with frontal lobe seizures treated with Trileptal and Keppra, who died 37 days after vaccination.

Most Frequently Reported Terms

Serious Reports (US), 12Sept2008–12Sept2009, Children 0–16 Years

MedDRA Preferred Term	No. Reports	Label
Headache	40	Listed
Syncope	37	Listed
Dizziness	36	Listed
Convulsion	32	Listed
Fatigue	30	Listed
Nausea	25	Listed
Pyrexia	25	Listed
Vomiting	23	Listed
Pain	21	Listed
Drug exposure during pregnancy	20	Listed
Abdominal pain*	20	Listed

* “Abdominal pain upper” is listed

Most Frequently Reported Terms

Non-Serious Reports (US), 12Sept2008–12Sept2009, Children 0–16 Years

MedDRA Preferred Term	No. Reports	Label
Syncope	211	Listed
Dizziness	198	Listed
Nausea	132	Listed
Headache	126	Listed
Pallor	115	Listed
Loss of consciousness	98	Listed
Pyrexia	95	Listed
Injection site erythema	76	Listed
Vomiting	75	Listed
Erythema	74	Listed

Conditions of Special Interest

Serious Reports (US), 12Sept2008–12Sept2009, Children 0–16 years

MedDRA Preferred Term	No. Reports	Label
Pulmonary embolism	4	Listed
Systemic lupus erythematosus	4	Listed
Guillain-Barre Syndrome	3	Listed
Juvenile arthritis	2	Listed
Rheumatoid arthritis	2	Listed
Cellulitis	1	Unlisted
Acute disseminated encephalomyelitis	1	Listed
Deep vein thrombosis	1	Listed
Optic neuritis	0	Listed
Autoimmune thyroiditis	0	Listed
Multiple sclerosis	0	Listed
Motor neuron disease	0	Listed

Pregnancy Registry

- 5 year regulatory commitment by Merck agreed upon at licensure

- Prospective observational study in US, Canada and France
  - Interim data from 1June2006 – 31May2009
  - Of 1,043 total vaccine-exposed pregnancies* with known outcomes, 64 miscarriages, 24 congenital anomalies, 10 fetal deaths
  - Females 9–15 years: 1/64 miscarriages
  - Females ≤16 years: 5/24 congenital anomalies, 3/10 fetal deaths

- Overall rate of congenital anomalies and miscarriages was within estimated background rate
- Review of congenital anomalies and deaths did not identify any unusual patterns

* Gardasil exposure defined as vaccination 1 month prior to last menstrual period or anytime during pregnancy

Pregnancy Registry

Congenital Anomalies, ≤ 16 Years

Anomaly	Maternal Age	Timing of Exposure from LMP (weeks)	Notes
Atrial septal defect	14	12	None reported
Gastroschisis	15	8.5	On sertraline; received Tdap 6 days after Gardasil
Atrial septal defect	15	3	25 week EGA, maternal smoking, Strattera use discontinued after becoming pregnant
Polydactyly	15	2	Positive family history of polydactyly
Pulmonic stenosis	16	4–8	Mildly dilated and hypertrophied right ventricle with good systolic function

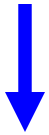
Pregnancy Registry

Reports of Fetal Deaths, ≤ 16 Years

Maternal Age	EGA at death (weeks)	Concomitant Medications	Timing of Exposure from LMP (weeks)	Notes
12	21	Birth control pills	5	Mother Rh negative, father Rh positive.
14	U	Methylphenidate	2.5	Reported as "delivered stillborn baby early"
15	24	Vitamins	8	Normal U/S at 19 weeks; fetal demise at 24 weeks. No fetal anomalies.

Changes to PI, Sept2008–Sept2009

"Syncope has been reported following vaccination with GARDASIL and **may result in falling with injury**; observation for 15 minutes after administration is recommended."



"Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, **sometimes associated with tonic-clonic movements and other seizure-like activity**, has been reported following vaccination with GARDASIL. **When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position**."

"Chills" added to postmarketing section

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Postmarketing Surveillance Framework

Active Surveillance

Safety Study in Females 9–26 years

Vaccine Safety Data Link

Safety Study in Males 9–26 years (new)

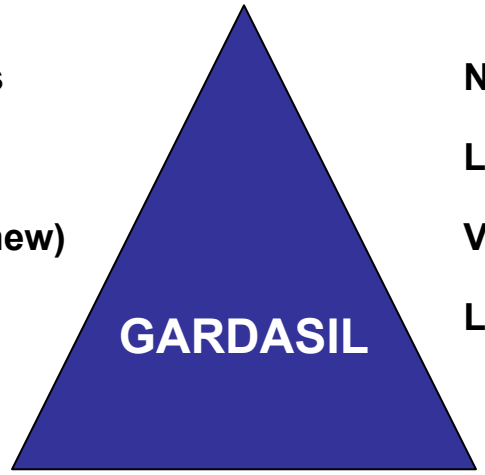
Registry-Based & Long Term Follow-Up Studies

Nordic Long Term Follow-Up Women

Long Term Follow-Up Adolescents

Vaccine Impact in Population

Long Term Follow-Up Males



Passive Surveillance (VAERS)
& Pregnancy Registry

Postlicensure Study Commitments by Merck*

Study	Study Design	Population	Safety-Related Objectives
Safety in Males aged 9–26 years	Active surveillance (N= ~135,000)	9–26 years	• ER visits, hospitalizations 0–60 days • New-onset autoimmune diseases 0–6 months
Nordic Long Term Follow-Up in Women	Registry-based study (N = 5,496)	16–23 years	Serious adverse events ≥14 years after start of vaccination, compared to published rates
Long Term Follow up in Males	Clinical trial extension (N = 2,025)	16–26 years	Serious adverse events 10 years after dose-1
Long Term Follow-Up Adolescents	Clinical trial extension (N = 1,078)	9–18 years	Serious adverse events and pregnancy outcomes 7–10 years after 3-doses
Vaccine Impact in Population	Population-based registry study	18–45 years	Congenital anomalies assessed in Denmark, Iceland, Norway, and Sweden. Incidence will be compared to the non-vaccinated population
PGRx Case Control Study in Females	Prospective case-control	14–26 years	Endpoints include: CNS demyelination, SLE, inflammatory arthritis, myositis, dermatomyositis, GBS, type 1 diabetes, autoimmune thyroiditis, graves disease, ITP.

*Bonanni et al. Vaccine 28(2010)4719–4730

Conclusions

- More than 600,000 doses of Gardasil have been actively monitored
  - Additional 135,000 doses will be actively monitored among males
  - Total of 7 ongoing postlicensure studies with safety endpoints
- Multiple safety-related changes to the PI have been made
- FDA will continue routine safety monitoring, as described

Does the advisory committee concur?

Acknowledgments

OBE

- Christopher Le
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- Elizabeth Valenti
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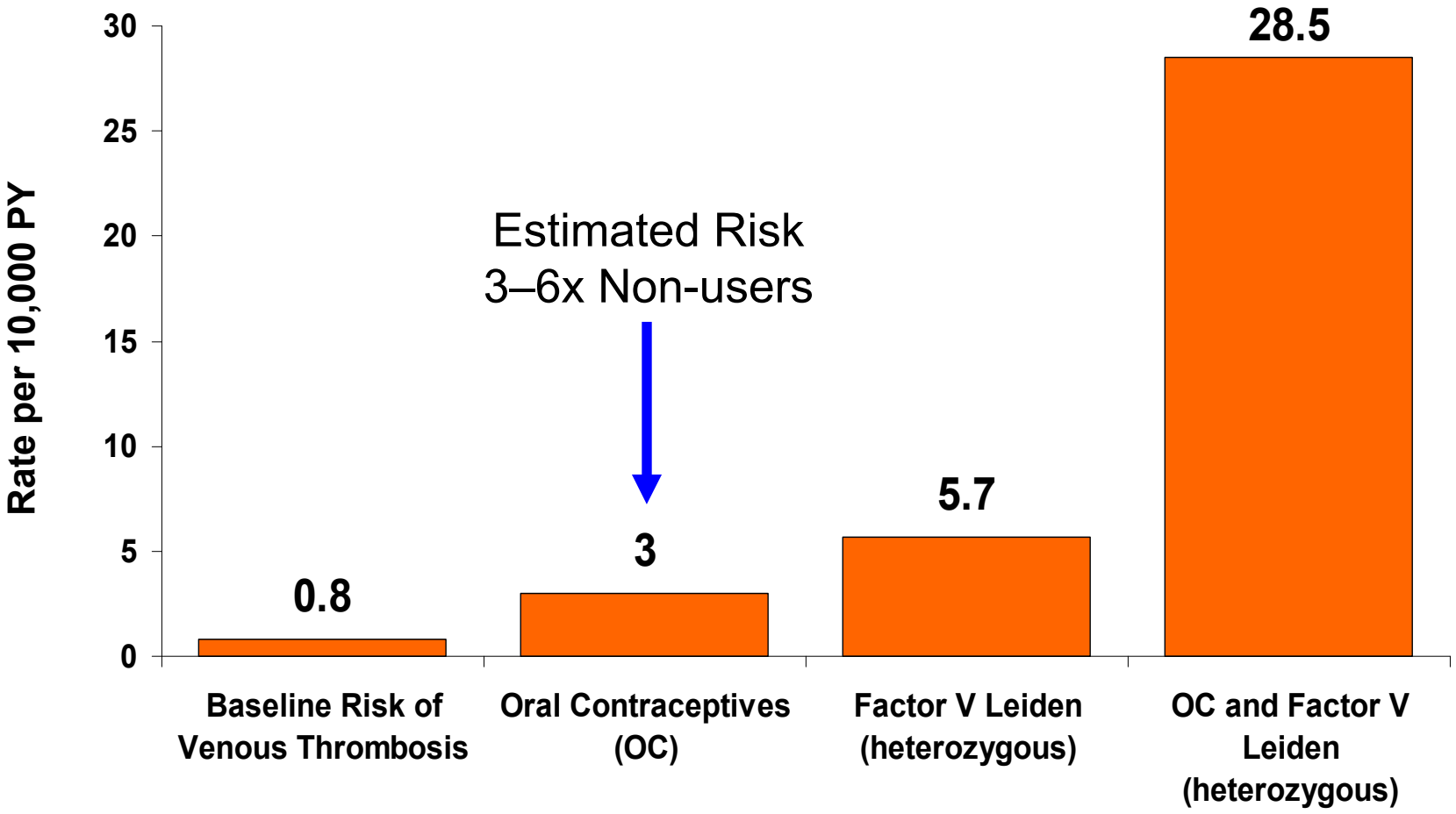
Back Up Slides

Risk of Venous Thrombosis



N Engl J Med. 2001 May 17;344(20):1527-35